

## **EXHIBIT B**

# BIODEGRADABLE HYDROGELS FOR DRUG DELIVERY

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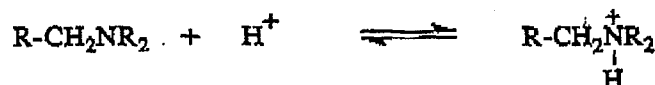
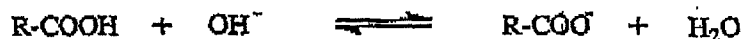
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van der Waals forces and polymer chains is great, it may be that molecular hydrogen bonding between the chains of cellulose is so strong that, after hydration, the rigidity of the polymer backbone prevents hydrolysis to result in degraded polymers, the polymerization of the polymer backbone, and the reduction in the weight degradation products from the body [29].

## 2.2.2 Charge Formation Followed by Dissolution

### 2.2.2.1 IONIZATION OR PROTONATION

Some polymers are initially water-insoluble but become solubilized by ionization or protonation of a pendant group. Examples are shown here.



Insoluble

Highly soluble

Polymers dissolve in water. Poly(styrene sulfonic acid), poly(styrene sulfonyl), and poly(styrene sulfonyl) readily dissolve in water by their polar molecules. Other polar polymers, such as poly(ethylene oxide) (PEO), readily dissolve in water by their polar groups.

The hydrophilic polymer in water forms a hydrogel [28]. This hydrogel is a loose network of polymer chains. Once a gel is formed, further addition of water, and individual polymer molecules are released, referred to as erosion or dissolution of the core and finally the gel dissolves. The dissolution rate of water-soluble polymers depends on molecular weight and stereochemistry.

The dissolution rate of water-soluble polymers depends on the amount of water, the concentration of polymer, the concentration at which the gel is formed, and vice versa by varying the amount of water, pH, or type of salt.

The solubility of polyacids is strongly pH-dependent. At low pH solution, polyacids are not water-soluble because the carboxyl groups of polyacids are protonated, i.e., not ionized. Upon an increase in the pH of the solution, the carboxyl groups release hydrogen atoms and become ionized. As the content of the ionized groups gradually increases, the polymer becomes more hydrophilic, absorbs water, swells, and finally dissolves in water. The solubility of polybases also strongly depends on pH, but the trend is opposite to that of polyacids. Polybases are water-soluble at low pH ranges.

Polyacids have been used widely as enteric coating materials for pharmaceuticals. They are poorly water-soluble in low pH environments, such as in the stomach, and dissolve in alkaline conditions such as those found in the intestines. The pH-sensitive polymers that have been used as enteric coating materials are shellac (esters of aleuritic acid), cellulose acetate phthalate, cellulose acetate succinate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose phthalate, and poly(methacrylic acid-co-methyl methacrylate) [32]. Among these, the most widely used polymers for enteric coating are cellulose acetate phthalate, poly(vinyl acetate phthalate), and poly(methacrylic acid-co-methyl methacrylate) [33,34]. The structures of these enteric coating polymers are shown in Figure 2.1. Cellulose acetate phthalate becomes water-soluble at a pH greater than 6, while poly(vinyl acetate phthalate) and hydroxypropylmethylcellulose phthalate are ionized at a lower pH [35].